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NEUROENDOCRINE EFFECTS OF HELMINTHIASES (A REVIEW)

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Nowadays the number of patients diagnosed with helminthiasis shows tendency for steady growth around the world. During last few years, researches in the field of immunology have again turned their attention towards the question of parasitological immunity and tissue response. Helminthiasis and other parasitic diseases in some instances can induce central nervous system disorders and violate human behavioral reactions. Studies have suggested an association between epilepsy and helminth infection, but a causal relationship is not established in many helminths, except perhaps with neurocysticercosis. The aim of this review is to reveal details of specific mechanisms of the general helminths' impact on the nervous system and the endocrine control level of physiological functions of the host organism. Finally, we discuss the current gaps in knowledge about the interaction between helminths, immunity, and human endocrine system.

Key words: helminths, immunity, hormones, cytokines.

НЕЙРОЭНДОКРИННЫЕ ПОСЛЕДСТВИЯ ГЕЛЬМИНТОЗОВ (ОБЗОР)

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Согласно данным литературы, количество пациентов с диагнозом «гельминтоз» демонстрирует тенденцию к неуклонному росту во всем мире. В данном обзоре уделено внимание результатам экспериментальных исследований, указывающих на то что нейро-психические нарушения у человека в условиях хронического течения паразитарных заболеваний, включая гельминтозы, могут быть вызваны не только прямыми нейротропными эффектами паразита, но и возникают вторично в результате повреждения других органов. Локализация гельминта в центральной нервной системе человека очень часто может приводить к психическим заболеваниям, тем не менее обоснованность взаимосвязи нейроцистицеркоза и эпилепсии у человека сохраняет статус дискуссионного вопроса. В связи с этим ряд авторов высказывают мысль о

том, что обсуждаемые явления необходимо рассматривать в комплексе взаимодействия нервной, эндокринной и иммунной систем.

Цель данной работы — выявить сведения о специфических механизмах влияния гельминтов на деятельность нервной системы и состояние эндокринного звена контроля физиологических функций организма хозяина. Проведенный обзор литературы показывает актуальность разнообразных нейро-эндокринных эффектов гельминтозов для современной медицины, хотя эта тема остается мало изученной.

Ключевые слова: гельминты, нервная система, иммунитет, гормоны, цитокины.

According to literary data, the number of patients diagnosed with helminthiasis shows a tendency for steady growth in the modern world (Garcia et al., 2014; Berkowitz et al., 2015; Morys et al., 2015). The distribution of helminth infections is heterogeneous and estimates show that developing regions of the world have the highest prevalence of helminthiasis. It is suggested that 2.2 billion people are infected with helminths, with the poorest bearing the brunt of the burden, particularly, for undetermined reasons, school-aged children. Numerous investigators have taken up this question from various points of view, using various hosts and parasites with the result that there has been amassed a large amount of suggestive data but little conclusive evidence either for or against the development of immunity to helminths. Moreover, the authors of the cited publications underline that the localization of helminths in the human central nervous system can very often lead to serious mental illness (Carpio, Romo, 2014; Othman et al., 2014). Epilepsy associated with helminths occurs throughout the world, with the prevalence higher in poor countries, particularly those in tropical regions. However, in our view, we should pay attention to several important points. Firstly, helminthiasis neurological effects may be recorded even in cases where mechanical damage to the nervous tissue by body covers of the helminth does not occur. Secondly, information about the neurotropic effects of helminths can be provoked by representatives found in all the major classes of helminths such as *Trematoda*, *Cestoda*, and *Nematoda*. Thirdly, the indirect impact of helminths is manifested not only in changes in the functional state of the nervous system but also at the level of endocrine regulation of the body's homeostatic parameters adjustment. Consequently, we are not talking about the specifics of the pathogenic properties of certain types of parasitic worms. Most likely, it is logical to consider the available data in this area of literature from the standpoint of one side of interaction aspects between parasite and host organisms (Escobedo et al., 2005; Bottasso, Morales-Montor, 2009; Escobedo et al., 2009).

Therefore, the aim of this review is to reveal details about the specific mechanisms of the helminths' impact on the nervous system and the endocrine control level of physiological functions in the host organism.

NEUROLOGICAL EFFECTS OF HELMINTH INFECTIONS

In our review we found it necessary to pay attention to the results of the recent experimental studies. Since, according to some authors neuro-psychiatric disorders in humans in a chronic course of parasitic diseases, including helminth infections can be caused not only by direct neurotrophic effects of the parasite, but there again, resulting in damage to other organ systems: kidneys, liver, circulatory system, lungs, etc. (Morys et al., 2015). It should be noted that the

comparison of clinical and experimental data led to some success in deciphering the pathogenic mechanisms of hippocampal sclerosis during neurocysticercosis that could lead to the development of epilepsy (Del Brutto et al., 2016). However, the validity of the relationship between neurocysticercosis and epilepsy in humans still maintains the status of the issue discussion (Carpio, Romo, 2014).

Therefore, on the one hand, these experimental observations allow us to judge the nature of helminth violations including the early stages of infestation more reliably. On the other hand, in these circumstances there is a question related to the extrapolation of experimental results on the person, which involves the development of specific methods of correction of violations in addition to helminth removal strategies (Escobedo et al., 2005; Dkhil et al., 2015). Finally, a number of authors have suggested that the phenomenon under discussion must be seen in the complex interaction between the nervous, endocrine and immune systems (Escobedo et al., 2009). The literature provides experimental evidence that in mice infected with *Schistosoma mansoni* there is a number of changes in the parameters of the cerebral functions: a violation of neurotransmitters production (norepinephrine and dopamine), specific changes in protein cells in the brain biosynthesis, synthesis decrease in glutathione, and increased production of a molecule of nitric oxide (Dkhil et al., 2015). It was found that migratory larvae of the nematode genus *Toxocara* are capable of causing crude lipid and protein metabolism violations in the mouse brain (Janecek et al., 2015).

According to the opinion of some researchers, the character of changes of protein biosynthesis processes in nerve cells may indicate selective inhibition of sensory systems and protective functions of the body. We argue that the totality of the effects observed may lead finally to neurodegenerative changes. The thesis that the functional changes in the nervous tissue as the result of current helminth infections can develop into gross structural abnormalities of the nervous tissue is expressed by other authors (Dkhil et al., 2015). Helminth-induced modulation of immune reactions in the nervous tissue, which is manifested in the early stages of the disease in changing of proinflammatory cytokines and interleukins production in the central nervous system is considered by some researchers as one of the pathogenetic mechanisms underlying this type of pathologies (López-Griego et al., 2015). The authors emphasize close relationship intensity of cytokine production and the state of interneuron transmission, emphasizing the presence of distinct gender-specific sensitivity of investigated indices in animals. Thus, it should be noted that the efficacy of anti-inflammatory therapy has been demonstrated indeed in the treatment of such dangerous helminthiasis as some severe neurocysticercosis (Zhao et al., 2016).

Another important aspect of the relations between host and parasite organisms is a problem of the parasite escape from the immune defense of the host organism. The literature suggests that helminths can escape from the immune defenses of the host, in particular, allowing neurocysticercosis to remain asymptomatic for a long time, and that get-away mechanism does not depend directly on the immunosuppressive cytokines (Chauhan et al., 2014; Sun et al., 2014). The cited publications contain information about endocrine factors of helminths that can directly induce the independent on cytokines immunity control escape implemented through selective inhibition of calcium channels of immune cells in the brain. In addition to the effectiveness of calcium channel blockers, we consider another escape mechanism that is not directly associated with the pro-

duction of cytokines and indicates a possible sensitivity to helminths nitric oxide molecule production in experiment (Alonso-Trujillo et al., 2007). At the same time, in the early course of helminthiasis there is a noticeable increase in the synthesis of nitric oxide in the brain tissues of animals (Dkhil et al., 2015). Perhaps modulation of nitric oxide patterns by inducible NO-synthase is possible to consider another pathogenetic mechanism of structural damage to nervous tissue such as activation of NO-synthase activity which may be accompanied by increased production of reactive oxygen and nitrogen, as well as the activation of peptides and aromatic amino acids nitrosylation processes forming, in its turn, products with the potent cytotoxic effect (Dolomatov, Sataieva, 2015). The listed above cascade reactions hypothesis indirectly confirms the result of the peroxidation products accumulation in the brain tissues during experimental helminthiasis (Dkhil et al., 2015).

Thus, the thesis of the specificity of tropic effects of helminth infections related to the central mechanisms of regulation of physiological functions of the host organism (Escobedo et al., 2005), in our opinion, has a powerful potential. We add that there is even more clearly apparent role of the integration of the nervous, endocrine and immune systems of the host in protection mechanisms, opposing nematode parasites in the wall of the small intestine (Hernández-Cervantes et al., 2013).

In literature, however, we find a few unexpected details that helminth infections can have a beneficial effect on the human body, for example, on a patient with multiple sclerosis. In particular, the systemic effects of immune suppression, typical of many helminths, may soften multiple sclerosis intercourse which has an autoimmune nature. According to researchers, this phenomenon may occur due to the helminth-dependent stimulation of IL-10 and cytokine pleiotropic action TGF- β , depressing cell-mediated immunity (Correale et al., 2008, 2012, 2014).

Understanding the mechanisms of helminth-induced immunosuppression, implemented by cytokines through the modulation of the B-lymphocytes activity may have clinical application in the treatment prospects of autoimmune diseases (Hussaarts et al., 2011).

Another important practical aspect of this topic, a problem of early diagnosis of helminth infections, should be briefly mentioned. The relevance of this issue in connection with the extreme danger of diseases and their asymptomatic course in the early stages is an independent subject of research (Garcia et al., 2014).

INFLUENCE OF HELMINTH INFECTIONS ON THE ENDOCRINE SYSTEM

Even the earliest publications regarding this aspect contain information that hormone production in the host organism is a very important factor for the life cycle of the parasite (Escobedo et al., 2005). Indeed, a little later, it was found that worms have the ability for the specific adaptations of their physiological needs towards tissue metabolism of host sex hormones (Morales-Montor et al., 2008), and have a significant impact on the secretion of sexual hormones and reproductive system in the host organism (Rodriguez-Dorantes et al., 2010). At the same time, the idea is expressed that the restructuring of sex steroid metabolism allows the parasite not only obtaining its own physiologically active subs-

tances, but also have an impact on behavioral responses of the host (Morales-Montor et al., 2008) along with modulating the activity of immune defense (Escobedo et al., 2009) via peptide hormones of the hypothalamic-pituitary axis (Kelley et al., 2007). Indeed, experimental studies confirm the important role of human hormones to run helminth development (Castellanos-Sánchez et al., 2009). Thus, on the one hand, it highlights the potential species-specific nature of the susceptibility of closely related species of worms in the host organism hormones (Escobedo et al., 2009). On the other hand, we accumulated arguments in favor of the literature opinion that human hormones can fulfill a very important role in the regulation of helminth life processes (Narbonne et al., 2015). Research in this area expands and acquires the fundamental character (Mayer et al., 2015). Deeper understanding of the role of endocrine regulation mechanisms in helminth life cycle, according to some authors, can create prospects for parasite control (Dissous, 2015). Indeed, the results of experimental studies have shown that androgens may have a damaging effect on certain types of tapeworms (Ambrosio et al., 2015). Also, promising results were obtained by the experimental inhibition of intracellular insulin signal molecules in some trematodes (You et al., 2015).

Returning to integrating the functions of the central nervous system, it is necessary to note the role of the direct influence of the hypothalamic-pituitary axis in the regulation of defense reactions of the body aimed at resistance controlling towards helminths (Hernández-Cervantes et al., 2013). We have found the effect on nematodes. However, hereinafter, this phenomenon has been confirmed regarding cestode parasites also inhabiting intestine (Quintanar-Stephano et al., 2015). In addition, tissue hormones role in the host response to the presence of helminths should be noted (Buckinx et al., 2015).

It is also pertinent to note that hormone therapy is increasingly used in the treatment of helminth infections. So, along with the well-known anti-inflammatory hormones used in the treatment of some of the most dangerous helminth infections (Tsai et al., 2015; Zhao et al., 2016), we have found information about the use of melatonin as a supplement debilitating systemic toxicity of anthelmintic drugs (Charão et al., 2015).

CONCLUSIONS

This literature review shows the relevance of various neuro-endocrine effects study of helminth infections for the modern medicine, although this subject still remains fully unexplored. The analysis of the published data demonstrates the following.

1. Central nervous system is a material substrate of integration regulatory systems (nervous, endocrine and immune) and may be affected due to specific impacts of helminths even if the parasites are localized outside the central nervous system.

2. Direct neurological effects of helminth infections are often realized through the modulation of the immune defense mechanisms present in the nervous tissue, leading to restructuring and violation of protein biosynthesis process and lipid metabolism, and disturbances of interneuron signal transduction mechanisms.

3. Endocrine system also possesses target-specific effects on helminths. Hormones of the host organism can be used by helminths in regulation of their own life cycle and neuroendocrine link can be subject of parasitic attacks due to its involvement in the system control of the body's reactions.

References

- Alonso-Trujillo J., Rivera-Montoya I., Rodriguez-Sosa M., Terrazas L. I. 2007. Nitric oxide contributes to host resistance against experimental *Taenia crassiceps* cysticercosis. *Parasitological Research*. 100 (6): 1341—1350.
- Ambrosio J. R., Valverde-Islas L., Nava-Castro K. E. et al. 2015. Androgens exert a cysticidal effect upon *Taenia crassiceps* by disrupting flame cell morphology and function. *PLoS One*. 10 (6): e0127928. doi: 10.1371/journal.pone.0127928
- Berkowitz A. L., Raibagkar P., Pritt B. S., Mateen F. J. 2015. Neurologic manifestations of the neglected tropical diseases. *Journal of Neurological Sciences*. 349 (1—2): 20—32.
- Bottasso O., Morales-Montor J. 2009. Neuroimmunomodulation during infectious diseases: mechanisms, causes and consequences for the host. *Neuroimmunomodulation*. 16 (2): 65—67.
- Buckinx R., Bagyanszki M., Avula L. R. et al. 2015. Expression of corticotropin-releasing factor and urocortins in the normal and *Schistosoma mansoni*-infected mouse ileum. *Cell and Tissue Research*. 359 (2): 453—463.
- Carpio A., Romo M. L. 2014. The relationship between neurocysticercosis and epilepsy: an endless debate. *Arquivos de Neuro-Psiquiatria*. 72 (5): 34—42.
- Castellanos-Sánchez V. O., Gómez-Conde E., Rocha-Gracia R. C. et al. 2009. Chorionic gonadotropin hormone receptors on *Taenia solium* and *Taenia crassiceps* cysticerci in culture. *Journal of Parasitology*. 95 (6): 1287—1294.
- Charao M. F., Souto C., Brucker N. et al. 2015. *Caenorhabditis elegans* as an alternative *in vivo* model to determine oral uptake, nanotoxicity, and efficacy of melatonin-loaded lipid-core nanocapsules on paraquat damage. *International Journal of Nanomedicine*. 10: 5093—5106.
- Chauhan A., Sun Y., Pani B. et al. 2014. Helminth induced suppression of macrophage activation is correlated with inhibition of calcium channel activity. *PLoS One*. 9 (7): 1023. doi: 10.1371/journal.pone.0101023
- Correale J., Farez M., Razzitte G. 2008. Helminth infections associated with multiple sclerosis induce regulatory B cells. *Annals of Neurology*. 64 (2): 187—199.
- Correale J., Farez M. F. 2012. Does helminth activation of toll-like receptors modulate immune response in multiple sclerosis patients? *Frontiers in Cellular and Infection Microbiology*. 24 (2): 112.
- Correale J., Equiza T. R. 2014. Regulatory B cells, helminths, and multiple sclerosis. *Methods in Molecular Biology*. 1190: 257—269.
- Del Brutto O. H., Engel J. Jr., Eliashiv D. S., Garcia H. H. 2016. Update on cysticercosis epileptogenesis: the role of the hippocampus. *Current Neurology and Neuroscience Reports*. 16 (1): 1.
- Dissous C. 2015. Venus kinase receptors at the crossroads of insulin signaling: their role in reproduction for helminths and insects. *Frontiers in Endocrinology*. 6: 118. doi: 10.3389/fendo.2015.00118
- Dkhil M. A., Bauomy A. A., Diab M. S. et al. 2015. Impact of gold nanoparticles on brain of mice infected with *Schistosoma mansoni*. *Parasitology Research*. 114 (10): 3711—3719.
- Dolomatov S. I., Sataieva T. P. 2015. Effect of ras-blockers and no-cycle metabolites on the renal functions of rats exposed to thyroxine injections. *Journal of Education, Health and Sport*. 5 (1): 41—55.
- Escobedo G., López-Griego L., Morales-Montor J. 2009. Neuroimmunoendocrine modulation in the host by helminth parasites: a novel form of host-parasite coevolution? *Neuroimmunomodulation*. 16 (2): 78—87.

- Escobedo G., Roberts C. W., Carrero J. C., Morales-Montor J. 2005. Parasite regulation by host hormones: an old mechanism of host exploitation? *Trends in Parasitology*. 21 (12): 588—593.
- Escobedo G., Romano M. C., Morales-Montor J. 2009. Differential *in vitro* effects of insulin on *Taenia crassiceps* and *Taenia solium* cysticerci. *Journal of Helminthology*. 83 (4): 403—412.
- García H. H., Nash T. E., Del Brutto O. H. 2014. Clinical symptoms, diagnosis, and treatment of neurocysticercosis. *Lancet Neurology*. 13 (12): 1202—1215.
- Hernández-Cervantes R., Quintanar-Stephano A., Moreno-Mendoza N. et al. 2013. Regulation of intestinal immune response by selective removal of the anterior, posterior, or entire pituitary gland in *Trichinella spiralis* infected golden hamsters. *PLoS One*. 8 (3): 586—596.
- Hussaarts L., van der Vlugt L. E., Yazdanbakhsh M., Smits H. H. 2011. Regulatory B-cell induction by helminths: implications for allergic disease. *Journal of Allergy and Clinical Immunology*. 128 (4): 733—739.
- Janecek E., Wilk E., Schughart K. et al. 2015. Microarray gene expression analysis reveals major differences between *Toxocara canis* and *Toxocara cati* neurotoxocarosis and involvement of *T. canis* in lipid biosynthetic processes. *International Journal of Parasitology*. 45 (7): 495—503.
- Kelley K. W., Weigent D. A., Kooijman R. 2007. Protein hormones and immunity. *Brain, Behavior and Immunity*. 21 (4): 384—392.
- López-Griego L., Nava-Castro K. E., López-Salazar V. et al. 2015. Gender-associated differential expression of cytokines in specific areas of the brain during helminth infection. *Journal of Interferon & Cytokine Research*. 35 (2): 116—125.
- Mayer M. G., Rödelberger C., Witte H. et al. 2015. The orphan gene dauerless regulates dauer development and intraspecific competition in nematodes by copy number variation. *PLoS Genetics*. 11 (6): e1005146. doi: 10.1371/journal.pgen.1005146
- Morales-Montor J., Escobedo G., Vargas-Villavicencio J. A., Larralde C. 2008. The neuroimmunoendocrine network in the complex host-parasite relationship during murine cysticercosis. *Current Topics in Medical Chemistry*. 8 (5): 400—407.
- Morys J. M., Jezewska M., Korzeniewski K. 2015. Neuropsychiatric manifestations of some tropical diseases. *International Maritime Health*. 66 (1): 30—35.
- Narbonne P., Maddox P. S., Labbé J. C. 2015. DAF-18/PTEN locally antagonizes insulin signalling to couple germline stem cell proliferation to oocyte needs in *C. elegans*. *Development*. 142 (24): 4230—4241.
- Othman A. A., Bruschi F., Ganna A. A. 2014. Helminth parasitic infections of the central nervous system: a diagnostic approach. *Journal of the Egyptian Society of Parasitologists*. 44 (1): 55—70.
- Quintanar-Stephano A., Hernández-Cervantes R., Moreno-Mendoza N. et al. 2015. The endocrine-immune network during taeniosis by *Taeniasolium*: The role of the pituitary gland. *Experimental Parasitology*. 159: 233—244.
- Rodríguez-Dorantes M., López-Griego L., Zarazúa-Cruz C. M., Morales-Montor J. 2010. Altered expression of cytokines and sex steroid receptors in the reproductive tract of cysticercotic male mice. *Parasite Immunology*. 32 (9): 91—100.
- Sun Y., Chauhan A., Sukumaran P. et al. 2014. Inhibition of store-operated calcium entry in microglia by helminth factors: implications for immune suppression in neurocysticercosis. *Journal of Neuroinflammation*. 11: 210.
- Tsai H. C., Lee B. Y., Yen C. M. et al. 2015. Dexamethasone inhibits brain apoptosis in mice with eosinophilic meningitis caused by *Angiostrongylus cantonensis* infection. *Parasites and Vectors*. 8: 200.
- You H., Gobert G. N., Cai P. et al. 2016. Suppression of the insulin receptors in adult *Schistosoma japonicum* impacts on parasite growth and development: further evidence of vaccine potential. *PLOS Pathogens*. 12 (7): e1005798.
- Zhao B. C., Jiang H. Y., Ma W. Y. et al. 2016. Albendazole and corticosteroids for the treatment of solitary cysticercus granuloma: a network meta-analysis. *PLoS Neglected Tropical Diseases*. 10 (2): e0004418.